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DELTAGEN, INC.
1031 Bing Street
San Carlos, CA 94070

EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/892,206	BRENNAN ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/24/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-37 and 41-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/24/2004 has been entered. Claims 34 has been amended. Claims 43-48 have been added. Claims 34-37 and 41-48 are pending and under consideration in the instant office action.

Non-compliant Claims Listing

The listing of the claims is not compliant with 37 CFR 1.121. Claim 41 is identifies as currently amended. However, no brackets, strikethroughs, underlinings or changes are noted. The claim should be identified as "previously presented".

Claim Objections

Claim 41 is objected to because of the following informalities: Claim 41 requires a pseudopregnant mouse to give birth. A pseudopregnant mouse is not pregnant and, therefore, cannot give birth. Appropriate correction is required.

Claim Rejections - 35 USC § 101/112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Definitions:
[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

See also the MPEP § 2107 - 2107.02.

Claims 34-37 and 41-48 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The rejection set forth on pages 2-6 of the previous office action mailed 06/25/2004 is maintained and applied to newly added claims 43-48 for reasons of record.

The instant specification has discussed that the mice of the instant invention can be used as models of disease to screen for drug therapies and as a tool for studying the function of a anaphylatoxin C3a receptor gene. As set forth in the previous office action, these uses fail to meet the standards of a specific, substantial and well-established utility required under 35 U.S.C. 101. In summary, the utilities provided by Applicant for the claimed mouse are not specific or substantial and therefore are not well established because the use of the mouse in screening for drugs to treat an unknown disease is not specific. The use for the claimed mouse in characterizing the function of an anaphylatoxin C3a receptor gene is not substantial. The basis for this rejection is further set forth in the previous office action and in the guidelines above.

Applicant has argued that the Patent Office guidelines state that a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose (pages 4-5). Applicant cites excerpts from an NIH website, Austin et al., Lewin's Genes VII and Albert's Molecular Biology of the Cell (pages 4-6 of Applicant's response) in establishing that knockout mice are invaluable tools of scientific research. Applicant also cites the MPEP in discussing the utility of research tools (pages 7-8 of Applicant's response; MPEP 2107.01, I). Applicant asserts that the claimed mouse can be used to study the association of the anaphylatoxin C3a receptor gene with reduced thymus weight,,

reduced thymus size, reduced thymus to body weight ration, increased susceptibility to seizure and/or a stimulus processing disorder (see page 8, paragraph 4). In general, Applicant does not understand how the invention cannot have utility when the invention is being used by one of skill in the art and has clearly been accepted as useful by several leaders in the field of transgenic technology.

In response, the instant invention has failed to meet the requirements of possessing a well-established utility and for a use with any particular practical purpose. A well-established utility and a utility with a particular practical purpose is one that is specific and substantial (see MPEP 2107(II)(A)(3)(ii) and MPEP 2107 (II)(B)(1)). The utility of the instant invention is neither specific nor substantial for reasons of record. Applicant is reminded that the utility guidelines (see above) expressly state that utilities requiring further research to identify or reasonably confirm a use do not define substantial utilities. Examples of uses that are not considered substantial utilities include basic research in studying the claimed product and use to screen for therapeutics for an unspecified disease. The use of the invention by the skilled artisan does not impart patentability or patentable use on the invention for reasons set forth above.

With specific respect to Applicant's applied references, the validity of the opinion of the NIH and Albert and the others cited with respect to the value of the knockout mouse in determining gene function is not questioned. However, the use of a mouse to determine gene function, as set forth above, does not meet the requirement that a utility be specific and substantial, and therefore, does not fulfill the requirements of utility under 35 USC 101. With respect to MPEP 2107.01, I, a gas chromatograph is a research tool with a well-defined

function and highly specific use that does not necessitate further study of itself. It may be that a gas chromatograph may be used for a wide variety of analyses; however, this does not change its specific use for analyzing a sample. In contrast, the claimed invention is not a general tool for analyzing other samples and, at most, serves to study the function of a single gene. In this respect, the utility of a knockout mouse cannot be compared to a gas chromatograph. Therefore, the utility of the instant invention is neither specific nor substantial.

Applicant also discloses the commercial use of the claimed mice and states that commercial use and acceptance is one important indication that the utility of an invention has been recognized by one of skill in the art (page 8 of Applicant's remarks).

In response, Applicant fails to provide description or evidence of such commercial use. Applicant has not provided any evidence pertaining to what the mice are being used for and therefore, without evidence to the contrary, it is assumed that the mice are being used for the uses of record, namely in screening for drugs to treat a non-specified disease, in studying gene function and in studying gene expression (see below). As set forth above and in the previous office action, theses uses are not specific or substantial.

Applicant has stated that the mice are useful for studying expression of the anaphylatoxin C3a receptor gene because the mice contain a lacZ reporter gene under the control of the anaphylatoxin C3a receptor gene promoter (page 11 of Applicant's response).

In response, this too is a general utility that applies to any knockout mouse and is not specific. It is a widely used technique to generate mouse knockouts by inserting a visible reporter gene into an endogenous gene. Just as any gene can be cloned to study gene expression, any gene can be knocked out to study function and/or expression.

Applicant has referred to the principles set forth in *In re Brana* (see pages 8-11 of Applicant's remarks). Applicant asserts that the specification supports a use of the knockout mouse that is specific and substantial in light of the teaching of *In re Brana.*

In response, the fact pattern in *Brana* does not correlate to the fact pattern of the instant application. In *Brana*, the court addressed two separate issues, utility and enablement. The court held that the specification did, in fact, disclose a specific and substantial use for the compound, treating leukemia, and that this use was overlooked by the PTO in making the rejection under 101. The court observed that the claimed compound was similar in structure to compounds in the prior art that were useful in treating leukemia. The claimed compound behaved in a manner similar to that of the prior art in art accepted assays for anti-leukemic activity. Therefore, the specification enabled the use. The instant specification and the art of record fail to support such a patentable utility for the instant invention and therefore, the principles set forth in *In re Brana* do not apply to the instant invention.

In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse and cells encompassed by the claims to be specific and substantial.

Claims 34-37 and 41-48 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The rejection of claims 34-37 and 41-42 is maintained for reasons of record as reiterated below and applied to newly added claims 43-48 (see pages 6-12 of the previous office action). New grounds of rejection based on newly added claims are set forth below as well.

1) Claim 42 was previously rejected as not being enabled by the specification as the claim broadly encompassed mice comprising a heterozygous disruption of the anaphylatoxin C3a receptor gene. This rejection is maintained and applied to the other pending claims as all claims 34-37 and 41-48 broadly encompass the heterozygous mouse wherein the heterozygous mouse exhibits any phenotype. Newly added claims 43-48 also encompass broadly a homozygous mouse wherein the mouse exhibits any phenotype. Claims 34 -36 also encompass homozygous mice wherein the mice exhibit reduced thymus size, reduced thymus weight, reduced thymus to body weight ratio, increased susceptibility to seizure and decreased prepulse inhibition. The specification purports that a phenotype of a lower required dose of metrazol to induce seizure stages in the homozygous mice (page 55, lines 10-13), decreased prepulse inhibition and reduced size and reduced weight of thymus of homozygous mutants compared to wild-type occurs in the homozygous mice.

Applicant has argued that the heterozygous mice are useful for studying gene expression.

While this use is not considered a patentable utility as set forth above, it would be considered a use for the mouse that is enabled by the specification if the claims required expression of a reporter mimicking anaphylatoxin C3a receptor gene expression. However, such a claim limitation is not present. The previous rejection is maintained as it relates to the claimed heterozygous mice exhibiting any phenotype for reasons of record and because the claims do not require reporter gene expression as argued by Applicant. Furthermore, with respect to the claims broadly encompassing any phenotype for either heterozygous (claims 34-37,43,44 and 46-48) or homozygous (claims 43 and 45-48 only), as set forth on pages 8-9 of

the office action mailed 02/13/2003, the phenotype of knockout mice is highly unpredictable and it would require undue experimentation for one of ordinary skill in the art to determine how to make and to use the claimed mice that exhibit any phenotype. The skilled artisan would not know how to make the claimed mice such that they exhibit any particular phenotype encompassed by the claims or know how how to use a mouse exhibiting any particular unknown phenotype.

Applicant has added the limitation of a null allele to the claims. This limitation does not obviate the above set-forth rejection. First, the specification does not demonstrate definitively that the anaphylatoxin C3a receptor disruption described creates a null allele wherein there is no gene activity. Gene disruptions can lead to hypomorphic and hypermorphic alleles. Second, even assuming a null allele is created, the heterozygous mouse has a wild-type allele and the phenotype of that mouse cannot be predicted. Finally, without a phenotypic limitation, the claims encompass any phenotype despite the recitation that the allele is null, including wild-type, and the specification does not teach how to make an anaphylatoxin C3a receptor knockout mouse such that it exhibits any of the other phenotypes encompassed by the claims. Therefore, this rejection is maintained and applied to claims 34-37,41 and 43-48 in addition to claim 42.

2) Claims 34-37 and 41-48 encompass any anaphylatoxin C3a receptor gene other than the anaphylatoxin C3a receptor gene that is encoded by the cDNA set forth by SEQ ID NO:1. The full breadth of these claims with respect to the genus of anaphylatoxin C3a receptor genes encompassed is not enabled.

The specification teaches only how to disrupt the endogenous genomic locus encoding the anaphylatoxin C3a receptor gene product that is also encoded by the cDNA set forth by SEQ ID NO:1. The specification does not teach how to disrupt any other anaphylatoxin C3a receptor gene in a mouse because the specification does not teach the sequence of any anaphylatoxin C3a receptor gene other than that encoding the same protein encoded by the cDNA set forth by SEQ ID NO:1. It would require undue experimentation for the a person of ordinary skill in the art to determine any other anaphylatoxin C3a genes and would require further experimentation to determine how to generate such a mouse exhibiting any of the claimed phenotypes.

3) The specification fails to enable the breadth of the claimed phenotypes of claims 34-36, 41 and 42. The claims encompass homozygous mice wherein the mice exhibit reduced thymus size, reduced thymus weight, reduced thymus to body weight ratio, increased susceptibility to seizure and a stimulus processing deficit. The specification purports that the claimed homozygous mice exhibit decreased prepulse inhibition but does not teach any other stimulus processing disorder as encompassed by the claims. The specification purports that the mice require a lower dosage of metrazol to reach seizure but does not teach that the mice have an increased susceptibility to seizure, especially when uniinduced as encompassed by the claims. The data given with respect to the thymus only demonstrates altered thymus size for male homozygotes. That data includes a data set of three. No statistical analysis accompanies of the data. At best the specification teaches that male mice have a smaller thymus and some number of mice exhibit a lower dosage requirement of metrazol to reach seizure-like response

and some number of homozygous mice exhibit a decreased PPI with a 90dB prepulse. The specification does not support any broader interpretation of phenotypes for these mice.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification and the unpredictability in the art of knockout mice, the skilled artisan would have to perform undue experimentation to determine how to make and use the claimed mice as claimed.

Written Description-New Matter

Claims 43-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The newly added claims contain the terminology "visible marker". Literal support for this terminology is not found in the specification.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 43-48 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re

Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added).

Newly added claim 43 recites that the mouse contains a null allele that comprises exogenous DNA comprises a gene encoding a visible marker. Claim 48 recites that the visible marker is lacZ. Applicant points to the specification for support of these amendments at page 8, lines 15-18 ; Figure 2B, and the original claims. These references in the specification fail to provide support for limitation of a visible marker in the newly added claims. Page 8, lines 15-18 defines the phrase "transgenic animal". Figure 2B describes the specific targeting construct indicating that the construct comprises both a positive selection marker and a lacZ gene, not just a lacZ as encompassed by claims 43-35 and 48.

The specification does not describe a genus of knockout mice wherein the targeting construct contains a generic "visible marker". In fact, the specification only shows that the lacZ gene was the only screenable marker contemplated and lacZ is not a visible marker, per

se. lacZ is a gene that encodes a product, β-galactosidase, the presence of which can be visualized indirectly through an assay that results in enzymatic production of a colored visible product. It is the product of the reaction that is visible, not the lacZ or the β-galactosidase. With respect to the visible marker, the specification does not mention, even in passing, a general feature of the claimed invention where the exogenous DNA encodes a visible marker, consequently, recitation of the limitation of "visible marker" in the current context is new matter. Applicant has not contemplated use of a visible marker. Furthermore, if lacZ were considered to be a visible marker, disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. See, for example, *In re Shokal*, 113 USPQ 283 (CCPA 1957); *Purdue Pharma L.P. v. Faulding Inc.,* 56 USPQ2d 1481 (CAFC 2000).

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42,46 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 is unclear because it refers to "the transgenic mouse produced by the method of claim 41". However, several different mice are produced while practicing the methods of claim 41. For example, step © produces a chimeric mouse and step (d) can produce a

heterozygous or homozygous mouse. It is not clear to which single mouse claim 42 is referring.

Claim 46 contains the limitation that the genome of the mouse of claim 43 comprises a gene encoding a selectable marker. Claim 43 requires that the genome of the mouse comprise a visible marker. It is unclear if the mouse of claim 46 further comprises a selection marker or if the selection marker is the visible marker or if the selection marker is meant to replace the visible marker of claim 43. Claim 47 depends from claim 46.

Claim 46 is further unclear because it uses the terminology "selection marker". It is unclear if the claim is referring to the terminology routinely used in the art of a "selectable marker" or if the claim is referring to some other type of marker. Claim 47 depends form claim 46.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 42-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (*Scientific American*, 1994, vol. 270, pp 34-41) in view of Tornetta (1997, J. Immunol., Vol. 158, pages 5277-5282).

Capecchi taught transforming a cell with a nucleic acid construct comprising a disruption in the HoxA-3 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous HoxA-3 locus, and using said cell to generate a mouse whose genome

comprises a disruption in the HoxA-3 gene. Capecchi differs from the claimed invention in that the targeting construct does not disrupt the anaphylatoxin C3a receptor gene.

However, at the time the claimed invention was made, Tornetta taught the cloning of the mouse anaphylatoxin C3a receptor gene (entire document and for further sequence detail GenBank Accession No. U77461).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make cells and a knockout mouse having a disruption in a targeted gene as taught by Capecchi wherein the gene was the anaphylatoxin C3a receptor gene as taught by Tornetta. One of ordinary skill in the art would have been sufficiently motivated to replace the Hox3A gene with the anaphylatoxin C3a receptor gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse. One of ordinary skill in the art would have been sufficiently motivated to disrupt the anaphylatoxin C3a receptor gene to determine its role in inflammatory disease, as described by Tornetta (page 5277, column 2, lines 3-8). Tornetta further supports the motivation to generate a transgenic mouse comprising a disruption n the anaphylatoxin C3a receptor gene based on the success of a similar disruption in the anaphylatoxin C5a receptor gene substantiating a role of the anaphylatoxin C5a receptor gene in inflammatory disease (Tornetta, page 5277, column 1, last 2 lines-column 2 lines 1-3).

The skilled artisan would have a reasonable expectation of success in combining the teachings of Capecchi and Tournetta because it was routine in the art to knock out any desired gene to determine the phenotypic effects of a specific gene disruption.

Note that absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning gene and the manifestation of disease (page 41, column 2, 2nd full paragraph).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

Joe Woitach
AU1632